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(54) Xanthine derivatives

Xanthin-Derivate

Dérivés de xanthine

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(73) Proprietor: **KYOWA HAKKO KOGYO CO., LTD.**
Chiyoda-ku, Tokyo-to (JP)

(72) Inventors:
- **Shimada, Junichi**
  Sunto-gun, Shizuoka-ken (JP)
- **Kuwabara, Takashi**
  Numazu-shi, Shizuoka-ken (JP)
- **Yasuzawa, Tohru**
  Sunto-gun, Shizuoka-ken (JP)
- **Magara, Hiroshi**
  Sunto-gun, Shizuoka-ken (JP)
- **Nonaka, Hiromi**
  Sunto-gun, Shizuoka-ken (JP)
- **Kusaka, Hideaki**
  Sunto-gun, Shizuoka-ken (JP)
- **Suzuki, Fumio**
  Mishima-shi, Shizuoka-ken (JP)

(74) Representative: **VOSSIUS & PARTNER**
Postfach 86 07 67
81634 München (DE)

(56) References cited:
EP-A- 0 001 735
EP-A- 0 415 456
EP-A- 0 501 379
EP-A- 0 541 120
EP-A- 0 560 354
US-A- 4 755 517

- **PATENT ABSTRACTS OF JAPAN vol. 17, no. 63 (C-1024) 8 February 1993 & JP-A-04 270 222 (KYOWA HAKKO KOGYO CO LTD) 25 September 1992**

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The file contains technical information submitted after the application was filed and not included in this specification

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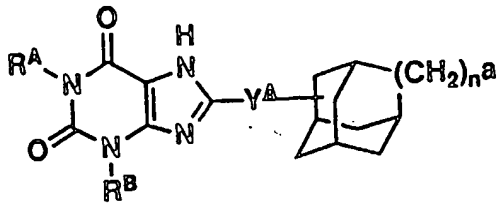
Description

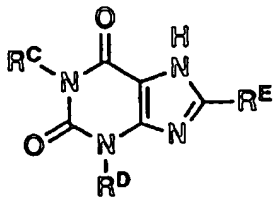
The present invention relates to xanthine derivatives or pharmaceutically acceptable salts thereof having adenosine A_1 receptor antagonizing activity, and thus exhibiting a diuretic effect, a renal-protecting effect, a bronchodilatory effect, a cerebral function improving effect, and an anti-dementia effect.

In relation to the compounds of the present invention, 8-(1-adamantyl)-1,3,7-trimethylxanthine is disclosed in Tetrahedron Letters, 27, 6337 (1986). However, nothing is mentioned on its pharmacological effect in the literature.

Also, it is known that a xanthine derivative represented by the formula

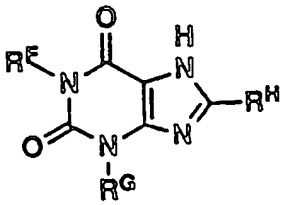


(wherein R^A and R^B are lower alkyl, Y^A is a single bond or alkylene, and n^a is 0 or 1) selectively antagonizes the adenosine A_1 receptor and thus shows a renal-protecting effect, and a bronchodilatory effect (Japanese Published Unexamined Patent Application No. 173889/91); and cerebral function improving effect (Japanese Published Unexamined Patent Application No. 270222/92). Further, it is known that a xanthine derivative represented by the formula

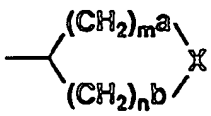


(wherein R^C and R^D are hydroxy-substituted or unsubstituted lower alkyl, and R^E is substituted or unsubstituted tricycloalkyl of C_7 - C_{12}) shows an anti-ulcerative effect, etc. (Japanese Published Unexamined Patent Application No. 58913/93), but no specific examples of the hydroxy-substituted xanthine derivatives are disclosed in the publication.

It is also known that a xanthine derivative represented by the formula

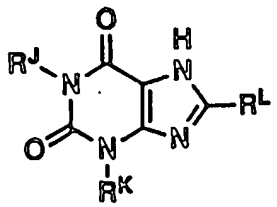


(wherein, R^F and R^G are the same or different, and each represent hydroxy-substituted or unsubstituted lower alkyl and R^H is dihydroxyalkyl or

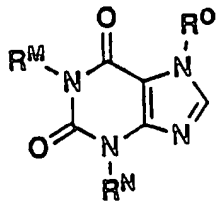


[wherein, X is O, S or NR^P (wherein R^P is hydrogen, lower alkyl or lower acyl), m^a and n^b are the same or different and

each represent an integer of from 1 to 5]) shows a central nervous system stimulating effect (US Patent No. 4755517). It is known that a xanthine derivative represented by the formula



(wherein, R^J is methyl, ethyl or propyl, R^K is 2-hydroxypropyl, and R^L is methyl or propyl) shows an antiallergic effect (Japanese Published Unexamined Patent Application No. 79296/79) and that a xanthine derivative represented by the formula

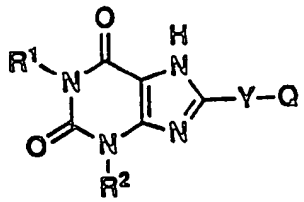


[wherein at least one of R^M and R^O is (ω-1)-hydroxyalkyl having from three to eight carbon atoms, or when only one of R^M and R^O is (ω-1)-hydroxyalkyl, the other is hydrogen or lower alkyl, and R^N is lower alkyl] reduces nephrotoxicity (Japanese Published Unexamined Patent Application No. 90028/91).

In EP-A-0 501 379, EP-A-0 560 354 and EP-A-0 541 120 xanthine derivatives are disclosed.

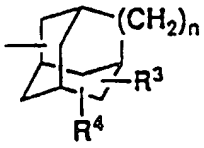
An object of the present invention is to provide a xanthine derivative and a pharmaceutically acceptable salt thereof having adenosine A_1 receptor antagonizing activity and thus exhibiting a diuretic effect, a renal-protecting effect, a bronchodilatory effect, a cerebral function improving effect and an anti-dementia effect.

In accordance with the present invention, there is provided a xanthine derivative represented by the formula (I) [which is hereinafter referred to as Compound (I) and the same applies to the compounds of other formula numbers]

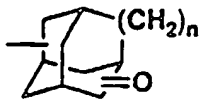


(I)

[wherein R^1 and R^2 are the same or different and each represent hydroxy-substituted, oxo-substituted or unsubstituted lower alkyl, Y is a single bond or alkylene, and Q is



(wherein R^3 and R^4 are the same or different and each represent hydrogen or hydroxy, n is 0 or 1, and when both R^3 and R^4 are hydrogen, at least one of R^1 and R^2 is hydroxy-substituted or oxo-substituted lower alkyl), or



(wherein n has the same meaning as defined above)] or a pharmaceutically acceptable salt thereof.

In the definition of Compound (I), the lower alkyl means a straight or branched alkyl having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl and hexyl; and the alkylene means a straight or branched alkylene having 1 to 4 carbon atoms such as methylene, ethylene, trimethylene, tetramethylene, methylmethylene, propylene, ethylethylene and the like. Each of R^1 and R^2 is optionally substituted with one to 2 substituents which is/are independently selected from the group consisting of hydroxy and oxygen.

As preferred examples of R^1 and R^2, 2- or 3- hydroxy-substituted propyl; 2- or 3- oxo-substituted propyl; and unsubstituted propyl may be mentioned. In the definition of Q, as the site where Q is bonded to Y, any position can be selected arbitrarily, and hydroxy and oxygen as the substituent can be situated in any position. A preferred example of Q includes 3-tricyclo[3.3.1.$0^{3,7}$]nonyl which is optionally substituted by hydroxy or oxygen at the 9-position or 6-position, and 1-tricyclo[3,3,1.$1^{3,7}$]decyl which is optionally substituted by hydroxy or oxygen at the 3-position.

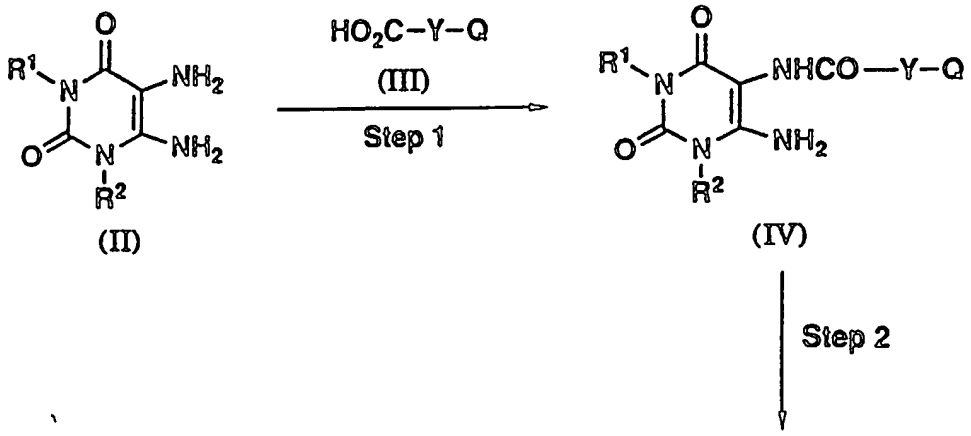
The pharmaceutically acceptable salts of Compound (I) include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, pharmaceutically acceptable ammonium salts, pharmaceutically acceptable organic amine addition salts, and pharmaceutically acceptable amino acid addition salts.

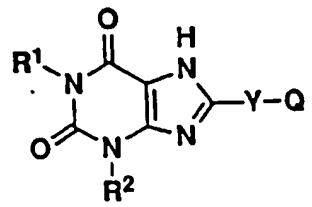
The pharmaceutically acceptable acid addition salt of Compound (I) includes inorganic acid addition salts such as the hydrochloride, sulfate and phosphate salt; and organic acid addition salts such as acetate, maleate, fumarate, tartrate and citrate salt. The pharmaceutically acceptable metal salt includes alkali metal salts such as the sodium salt and potassium salt, alkaline earth metal salts such as the magnesium salt and calcium salt, as well as the aluminium salt and zinc salt. The pharmaceutically acceptable ammonium salt includes the ammonium salt and tetramethyl ammonium salt. The pharmaceutically acceptable organic amine addition salt includes salts with morpholine and piperidine, and the pharmaceutically acceptable amino acid addition salt includes salts with lysine, glycine and phenylalanine.

The processes for preparing Compound (I) are described as follows.

Preparation Process 1:

Compound (I) can be prepared by the following reaction steps:





(I)

(wherein, R^1,R^2,Y and Q have the same meanings as defined above).

Step 1:

Compound (IV) can be obtained by reacting an uracil derivative (II) obtained by a known method, for example, the method as disclosed in Japanese Published Unexamined Patent Application No.79296/79, with a carboxylic acid (III) or a reactive derivative thereof.

As for the carboxylic acid (III) wherein n is 1, it can be prepared by the method as described in the following literature.

3-Hydroxyadamantane-1-carboxylic acid: Syn. Commun., 18, 1967 (1988).

2-Hydroxyadamantane-1-carboxylic acid and 4-hydroxy adamantane-1-carboxylic acid: J. Org. Chem., 38, 3447 (1973).

2-Oxoadamantane-1-carboxylic acid: J. Chem. Soc. Perkin I, 1893 (1976).

4-Oxoadamantane-1-carboxylic acid: J. Org. Chem., 48, 1099 (1973).

As for the carboxylic acid (III) wherein n is 0, it can be prepared by the method as described in the following literature.

9-Hydroxytricyclo [3.3.1.$0^{3,7}$]nonane-3-carboxylic acid (9-hydroxynoradamantane-3-carboxylic acid): J. Chem. Soc. Perkin I, 1669 (1973).

1-Hydroxytricyclo[3.3.1.$0^{3,7}$]nonane-3-carboxylic acid: J. Org. Chem., 48, 5231 (1983).

2-Hydroxytricyclo [3.3.1.$0^{3,7}$]nonane-2-carboxylic acid: Synthesis, 74 (1980).

9-Oxotricyclo[3.3.1.$0^{3,7}$]nonane-3-carboxylic acid: Chem. Ber., 103, 863 (1970).

9-Oxotricyclo[3.3.1.$0^{3,7}$]nonane-1-carboxylic acid: J. Am. Chem. Soc., 113, 6607 (1991).

6-Oxotricyclo[3.3.1.$0^{3,7}$]nonane-3-carboxylic acid is a new compound, which is prepared by a process shown in Reference example hereinafter.

As the reactive derivative of Compound (III), acid halides such as acid chloride and acid bromide may be mentioned; active esters such as p-nitrophenylester and N-oxysuccinimide; commercially available acid anhydrides or acid anhydrides produced by the use of carbodiimide such as 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, diisopropylcarbodiimide and dicyclohexylcarbodiimide; and acid anhydrides mixed with carbonic acid monoethyl ester and carbonic acid monoisobutyl ester and the like.

The reaction, wherein Compound (III) is used, is carried out at 50 to 200 °C in the absence of a solvent, and completed in 10 minutes to 5 hours.

The reaction, wherein a reactive derivative of Compound (III) is used, is carried out by a method similar to those generally used in peptide chemistry. That is, Compound (IV) can be obtained by reacting Compound (II) with a reactive derivative of Compound (III), preferably in the presence of an additive or a base. As the reacting solvent, halogenated hydrocarbons such as methylene chloride, chloroform and ethylene dichloride; ethers such as dioxane and tetrahydrofuran; dimethylformamide and dimethylsuifoxide, and if necessary water and the like may be mentioned. The additive is exemplified by 1-hydroxybenzotriazole and the like. The base is exemplified by pyridine, triethylamine, 4-dimethylaminopyridine, N-methylmorpholine and the like. The reaction is carried out at -80 to 50 °C and completed in 30 minutes to 24 hours. The reactive derivative can be used as such without isolation after it has been produced in the reaction system.

Step 2:

Compound (I) can be obtained by treating Compound (IV) with a base (method A), by treating Compound (IV) with a dehydrating agent (method B) or by heating Compound (IV) (method C).

In method A, as the base, an alkali metal hydroxide such as sodium hydroxide and potassium hydroxide and an alkaline earth metal hydroxide such as calcium hydroxide may be mentioned. As the reaction solvent, water, a lower alcohol such as methanol and ethanol, an ether such as dioxane and tetrahydrofuran, dimethylformamide, dimethylsulfoxide and the like may be used alone or in combination. The reaction is carried out at 0 to 180 °C and completed

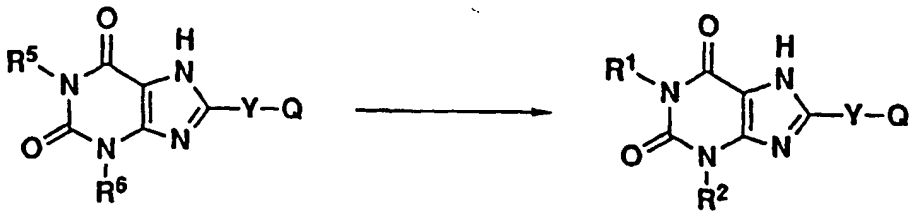
in 10 minutes to 6 hours.

In the method B, as the dehydrating agent, thionyl halide such as thionyl chloride, and phosphorus oxyhalide such as phosphorus oxychloride may be mentioned. The reaction is carried out in the absence of a solvent or in the presence of an inert solvent such as halogenated hydrocarbons (e.g.methylene chloride, chloroform and ethane dichloride), dimethylformamide and dimethylsulfoxide, at 0 to 180 °C and in 30 minutes to 12 hours.

In the method C, a polar solvent such as dimethylformamide, dimethylsulfoxide and Dow Thermo A (available from The Dow Chemical Co.) is used as the reaction solvent. The reaction is carried out at 50 to 200 °C and completed in 10 minutes to 5 hours.

Preparation Process 2:

Compound (I) can be prepared by the following reaction process.



(V) (I)

(wherein at least one of R^5 and R^6 is lower alkenyl, the other is lower alkyl and R^1, R^2, Y and Q have the same meanings as defined above).

The lower alkenyl as used herein means a straight or branched alkenyl having 2 to 6 carbon atoms, such as vinyl, allyl, propenyl, isopropenyl, butenyl and hexenyl, and the lower alkyl has the same meaning as defined above.

Compound (I) can be obtained by hydrating or oxidizing Compound (V) obtained by the above-mentioned Preparation Process 1, or according to the known method as described in Japanese Published Unexamined Patent Application No. 173889/91 or a method similar thereto. The hydration reaction can be carried out by the following four methods.

Method A: Compound (I) can be obtained by heating Compound (V) in a proton acid at 80 to 120 °C for 1 to 4 days. As the proton acid, dilute sulfuric acid, dilute nitric acid and aqueous perchloric acid and the like can be used.

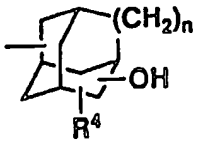
Method B: Compound (I) can be obtained by hydroborating Compound (V), followed by oxidation. Examples of the hydroborating agent are diborane (B_2H_6), its complexes (e.g. the tetrahydrofuran complex, the dimethylsulfide complex, the triethylamine complex and the like), diisoamylborane, t-hexylboran 9-borabicyclo[3.3.1]nonane (9-BBN) and the like. As the reaction solvent, ethers such as diglyme, tetrahydrofuran and diethyl ether can be used. The reaction is carried out at -30 to 50 °C and completed in 10 minutes to 12 hours. The oxidation reaction can be carried out by treating hydroborated Compound (I) with aqueous hydrogen peroxide in a mixed solvent of ethers such as diglyme, tetrahydrofuran and diethyl ether and an alkali aqueous solution at 0 to 50 °C for 10 minutes to 4 hours.

Method C: Compound (I) can be obtained by subjecting Compound (V) to the oxymercuration reaction with mercuric acetate and the like, followed by treatment with an alkali borohydride such as sodium borohydride. In the oxymercuration reaction, a mixed solvent of water and one of acetone, an ether and tetrahydrofuran is used as the solvent. The reaction is carried out at 0 to 50 °C and completed in 10 minutes to 12 hours. After the oxymercuration reaction is completed, the reaction mixture is alkalized, and reacted with an alkali metal borohydride at 0 to 30 °C for 10 minutes to 12 hours to produce Compound (I).

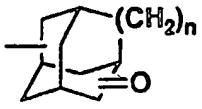
Method D: Compound (I) can be obtained by treating Compound (V) in the presence of a catalytic amount of palladium, with a re-oxidizing agent, in an oxygen atmosphere. Examples of the palladium catalyst include palladium chloride, bis(acetonitrile)palladium chloride, palladium sulfate, and bis(acetonitrile)nitropalladium chloride. Examples of the re-oxidizing agent are cuprous chloride, cupric chloride, cupric nitrate, cupric acetate or p-benzoquinone and the like. As the reaction solvent, ethers such as dioxane and tetrahydrofuran, dimethylformamide and water can be used alone or in combination. The reaction is carried out at 0 to 180 °C and completed in 10 minutes to 24 hours.

Preparation Process 3:

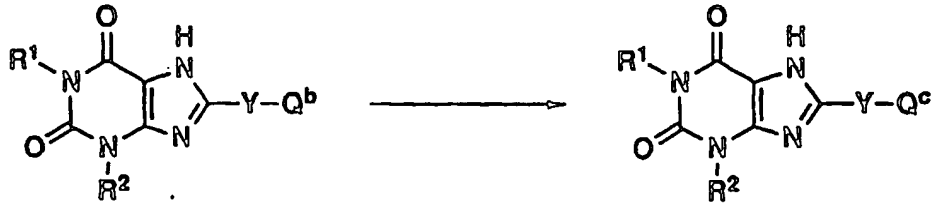
Compound (I-1), which is Compound (I) wherein Q is



(in which R^4 and n are previously defined), or

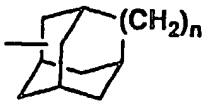


(wherein n is previously defined), can be produced by the following reaction process.

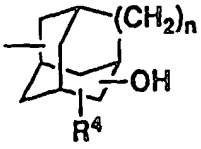


(I') (I-1)

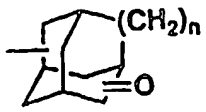
[wherein Q^b is a group in the definition of Q, represented by the following formula



(wherein n is previously defined);
Q^c is a group in the definition of Q, represented by the following formula



(wherein R^4 and n are previously defined)
or a group in the definition of Q, represented by the following formula



(wherein n is previously defined),
and R^1, R^2 and Y are previously defined].

Method A: Compound (I-1) can be obtained by subjecting Compound (I') to regio- or stereospecific hydroxylation or carbonylation in the presence of an appropriate oxidizing agent.

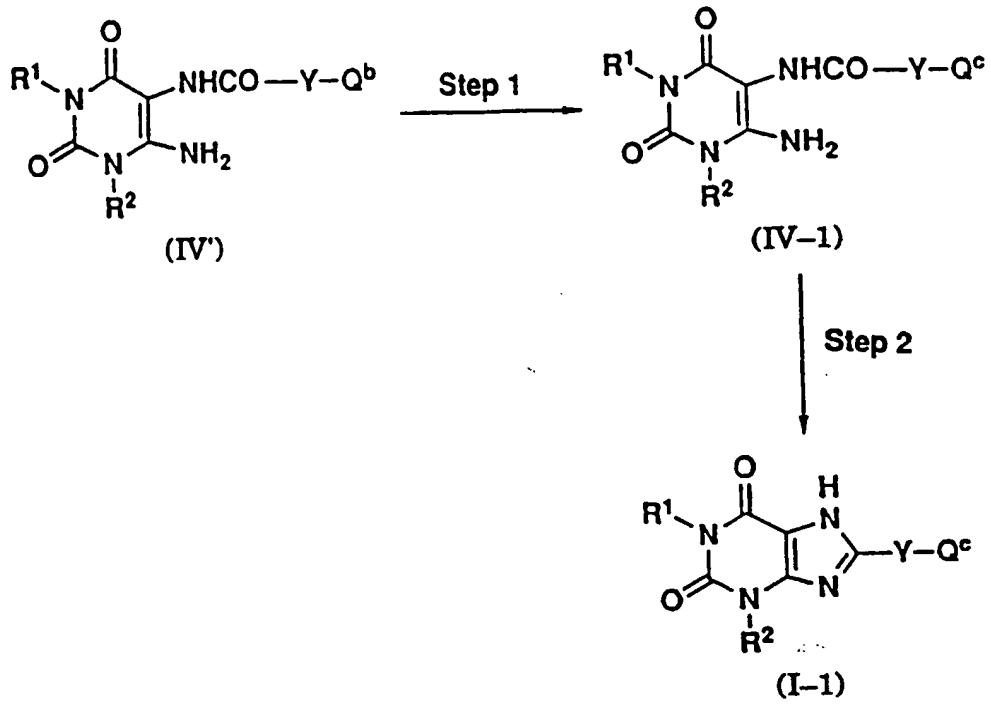
The oxidizing agent includes, for example, chromic anhydride, potassium permanganate, aqueous hydrogen peroxide, oxygen, ozone, nitric acid or organic peroxides such as tert-butyl hydroperoxide and dimethyl dioxirane. Further, ferrous chloride, ferric chloride, ferrous sulfate, ruthenium chloride and the like can be added, if necessary. The reaction solvent, depending on the sort of the oxidizing agent to be used, includes water, acetic acid, acetic anhydride, pyridine, benzene, acetonitrile and the like. The reaction is carried out at -50 to 150 °C and completed in 10 minutes to 96 hours.

Method B: Compound (I-1) can be obtained by suspending hepatocyte microsome obtained by the known method as described in Tetsuya Kamataki et al., (1985) "Applied Pharmacokinetics, Theory and Experiments" p.325, Edited by Manabu Hanano et al., Soft Science Co., Tokyo, in a neutral phosphate buffer, adding dihydronicotinamide adenine dinucleotide phosphate (NADPH) or an NADPH-generating reaction system thereto, and incubating the resulting mixture together with Compound (I') preferably in the presence of bovine serum albumin and a stabilizing agent.

As the hepatocyte microsome, that derived from a rat to which an inducer of a drug metabolic enzyme such as Phenobarbital Sodium have been administered, is preferably employed. The NADPH-generating system is not specifically limited, and an example is a mixed solution of 8 mM sodium β-nicotinamide adenine dinucleotide phosphate (β-NADP), 80 mM sodium glucose-6-phosphate, 10 units of glucose 6-phosphate dehydrogenase (derived from yeast; Oriental Yeast Co., Ltd.) and 60 mM magnesium chloride. As the stabilizing agent, any agent which can inhibit the lipid peroxidation of the hepatocyte microsome to stabilize the drug metabolic enzyme can be used, and one example is disodium ethylenediamine tetraacetate (EDTA). The incubation is carried out at 30 to 40 °C, preferably at 37 °C and the reaction is completed in 10 minutes to 24 hours.

Preparation Process 4:

Compound (I-1) can also be prepared by the following reaction steps



(IV') (IV-1) (I-1)

(wherein R^1, R^2, Y, Q^b and Q^c have the same meanings as defined above).

Step 1:

Compound (IV') prepared by a method similar to the Preparation Process 1 - Step 1 is subjected to an oxidation reaction similar to that described in Preparation Process 3 to provide Compound (IV-1), which is Compound (IV) in which Q is Q^c.

Step 2:

Compound (I-1) is obtained by cyclizing Compound (IV-1) in a manner similar to that described in Preparation Process 1 - Step 2.

The desired compounds in the processes described above can be isolated and purified by purification methods conventionally used in organic synthetic chemistry such as filtration, extraction, washing, drying, concentration, recrystallization and various kinds of chromatography.

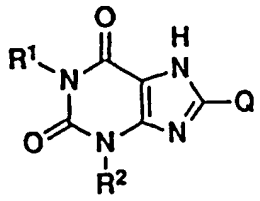
In the case where a salt of Compound (I) is desired, and it is produced in the form of the desired salt, the product as such can be subjected to purification. In the case where Compound (I) is produced in the free form and its salt is desired, Compound (I) is dissolved or suspended in a suitable solvent, followed by addition of an acid or a base to form a salt.

Compound (I) and the pharmaceutically acceptable salt thereof may also be in the form of adducts with water or various solvents, and the addition products are within the scope of this invention.

Compound (I) can exist in the form of optical isomers and the present invention covers all possible stereoisomers and mixtures thereof.

Representative examples of Compound (I) are shown in Table 1.

Table 1



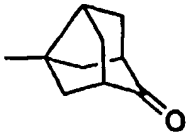
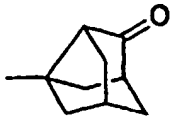
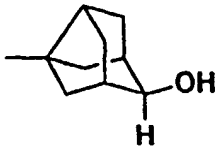
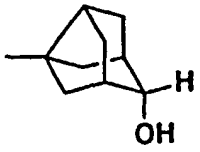
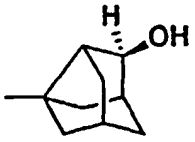
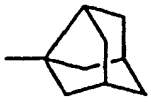
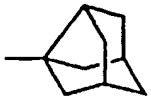
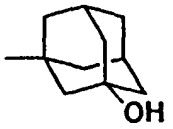
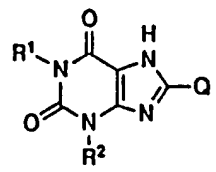
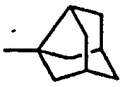
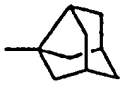
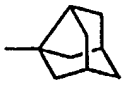
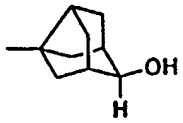
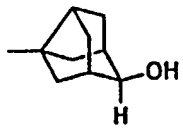
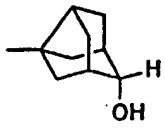
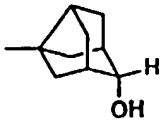
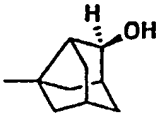
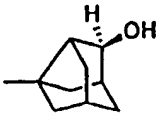
Compound	R^1	R^2	Q
1	*n*-C_3H_7	*n*-C_3H_7	
2	*n*-C_3H_7	*n*-C_3H_7	
3	*n*-C_3H_7	*n*-C_3H_7	
4	*n*-C_3H_7	*n*-C_3H_7	
5	*n*-C_3H_7	*n*-C_3H_7	
6	*n*-C_3H_7	$HOCH_2CH_2CH_2$-	
7	*n*-C_3H_7	$CH_3CH(OH)CH_2$-	
8	*n*-C_3H_7	*n*-C_3H_7	

Table 1-2



Compound	R^1	R^2	Q
9	$CH_3C(=O)CH_2$-	*n*-C_3H_7	
10	$CH_3CH(OH)CH_2$-	*n*-C_3H_7	
11	$O=CHCH_2CH_2$-	*n*-C_3H_7	
12	$CH_3C(=O)CH_2$-	*n*-C_3H_7	
13	$CH_3CH(OH)CH_2$-	*n*-C_3H_7	
14	$CH_3C(=O)CH_2$-	*n*-C_3H_7	
15	$CH_3CH(OH)CH_2$-	*n*-C_3H_7	
16	$CH_3C(=O)CH_2$-	*n*-C_3H_7	
17	$CH_3CH(OH)CH_2$-	*n*-C_3H_7	

Compound (I) and the pharmaceutically acceptable salt thereof have adenosine A_1 antagonizing activity, and thus exhibit a diuretic effect, and a renal-protecting effect, and anti-dementia effect. Compounds (I) and the pharmaceutically acceptable salts thereof are expected to be useful as a diuretic agent, a hypotensive agent and an anti-edematous

agent with a diuretic effect, as well as a renal-protecting agent to prevent and treat nephrotoxicity, to protect renal function, to prevent and treat nephritis, and to prevent and treat nephrotic syndrome.

Compound (I) and the pharmaceutically acceptable salt thereof further show a bronchodilatory effect, a cerebral function improving effect and an anti-dementia effect.

The pharmacological activities of Compound (I) are illustrated by the following test examples.

Test Example 1 Acute Toxicity Test

Test compounds Nos. 1 to 17 were orally administered to groups of dd-strain male mice weighing 20 ± 1 g, each group consisting of three mice. Seven days after the administration, the minimum lethal dose (MLD) of each compound was determined by observing the mortality.

Test compounds Nos. 1 to 17 showed a MLD of >300 mg/kg, and thus can be safely used in a wide range of doses.

Test Example 2 Adenosine Receptor Antagonizing Activity (Adenosine A_1 Receptor Binding Test)

The test was conducted according to the method of Bruns et al. [Proc. Natl. Acad. Sci. U.S.A., 77, 5547 (1980)] with slight modifications.

The Corpus striatum of a rat was suspended in ice-cooled 50 mM Tris hydroxymethyl aminomethane hydrochloride (Tris HCl) buffer (pH 7.7)by using a Polytron homogenizer (manufactured by Kinematicas Co.). The suspension was centrifuged (50,000 x g, 10 minutes), and the precipitate was suspended again in the same amount of 50 mM Tris HCl buffer. The suspension was centrifuged under the same conditions, and the final precipitate was suspended once again in 50 mM Tris HCl buffer to give a tissue concentration of 100 mg (wet weight)/ml. The tissue suspension was allowed to stand in the presence of 0.02 unit/mg tissue of adenosine deaminase (manufactured by Sigma Co.) at 37 °C for 30 minutes. The tissue suspension was centrifuged (50,000 x g, 10 minutes) and to the obtained precipitates 50 mM Tris HCl buffer was added to give a tissue concentration of 10 mg (wet weight)/ml.

To 1 ml of the tissue suspension thus prepared, 50 µl of cyclohexyladenosine labeled with tritium were added (^{3}H-CHA: 27 Ci/mmol, manufactured by New England Nuclear) (final concentration: 1.1 nM), and 50 µl of a test compound. The resulting mixture was allowed to stand at 25 °C for 90 minutes and then rapidly filtered by suction through a glass fiber filter (GF/C, manufactured by Whatman Co.). The filter was immediately washed three times with 5 ml each of ice-cooled 50 mM Tris HCl buffer, and transferred to a vial, and scintillator (EX-H by Wako Pure Chemical Industries, Ltd.) was added thereto. The radioactivity on the filter was determined with a liquid scintillation counter (manufactured by Packard Instrument Co.).

The inhibition rate (Ki value) of the test compound against the binding of A_1 receptors (^{3}H-CHA binding) was calculated by the equation of Cheng-Prusoff.

$$\text{Inhibition Rate (\%)} = \left(1 \times \frac{[B]-[N]}{[T]-[N]}\right) \times 100$$

[Notes]

1. "B" means the amount of radioactivity of ^{3}H-CHA bound in the presence of a test compound at various concentrations.
2. "T" means the amount of radioactivity of ^{3}H-CHA bound in the absence of a test compound.
3. "N" means the amount of radioactivity of ^{3}H-CHA bound in the presence of 10 µM N^6-(L-2-phenylisopropyl) adenosine (Sigma Co.).

Table 2

Test Compound	Ki (nM)
1	0.37
2	0.59
3	0.23
4	0.31
5	0.24
6	0.96

Table 2 (continued)

Test Compound	Ki (nM)
7	6.1
8	5.1

Test Example 3 Diuretic Effect

The experiment was performed by using Wistar rats (male; 150 to 300 g). The rats were starved for 18 hours prior to the administration of a test compound (n=4 to 5). After test compounds were dissolved in 0.4 % methanol, 1 % dimethylsulfoxide and 0.01 N sodium hydroxide/physiological saline, and administered intravenously, the physiological saline (25 ml/kg) was orally administered. Alternatively, test compounds dissolved in physiological saline (25 ml/kg) was orally administered to the rats. Urine was collected from the rats during 4 hours after the oral administration, and urine volume was measured by a graduated measuring cylinder, and the electrolytes in the urine (Na^+ and K^+) were determined by flame photometer (775 A manufactured by Hitachi, Ltd.). The results are shown in Tables 3 and 4.

Table 3

Test Compound	Dose (μg/kg,iv) (n=5)	Amount of urine (ml/kg)	Amount of Na^+ excreted (mEq/kg)	Amount of K^+ excreted (mEq/kg)	Na^+/K^+
Control group	-	14.5±1.8	2.23±0.61	1.47±0.31	1.52
3	3	26.4±0.6**	3.71±0.12*	1.24±0.10	2.99

*p<0.05;
**p<0.01 (Dunnett's test)

Table 4

Test Compound	Dose (mg/kg,po) (n)	Increase in amount of urine Δ (%)	Increase in amount of Na^+ excreted Δ(%)	Increase in amount of K^+ excreted Δ (%)	Na^+/K^+
Control Group	-(4~5)	0	0	0	1.00
1	0.01(5)	149	144	37	1.78
1	1.6(5)	258	193	36	2.15
2	0.1(5)	211	177	32	2.10
2	1.6(5)	241	188	8	2.67
3	0.01(4)	99	139	11	2.16
3	0.1(4)	105	148	-9	2.72
4	0.01(5)	200	167	43	1.86
4	1.6(5)	232	180	35	2.07
5	0.1(5)	134	107	12	1.85
5	1.6(5)	297	220	15	2.77
6	0.025(5)	134	111	5.1	2.00
6	0.1(5)	396	276	24	3.03
7	0.01(5)	140	97	33	1.48
7	0.1 5	200	138	23	1.93

From Tables 3 and 4, test compounds were found to have high Na-diuretic effect.

Test Example 4 Renal-protecting Effect (Glycerol-Induced Renal Failure Model)

A renal failure is a state where the renal function is lowered and the homeostasis of the body fluids can be no longer maintained. It is known that an acute renal failure characteristic of uriniferous tubule disorder is caused by subcutaneous or intramuscular injection of glycerol to rats [Can. J. Physiol. Pharmacol., 65, 42 (1987)].

Male Wistar rats were kept deprived of water for 18 hours, and served for the test. A test compound was intraperi-

toneally administered to the rats (dosage: 0.1 ml/100 g). After 30 minutes, the rats were anesthetized with ether and 50% glycerol was subcutaneously administered (dosage: 0.8 ml/100 g) to the rats, pinching the dorsal skin. Twenty four hours after the administration of glycerol, the rats were anesthetized with ether and 5 ml of blood was collected from the abdominal aorta. The collected blood was allowed to stand for 30 minutes or longer and then centrifuged at 3,000 rpm for 10 minutes, and the amounts of the serum creatinine and the serum urine-nitrogen (UN) were determined by auto analyzer (Olympus AU510) [creatinine test (Jaffé method), UN test (enzyme method); both tests were carried out. using Olympus AU500/550 exclusive reagent KATAYAMA].

The test results were analysed statistically [test of significance, Student's t-test (n=8~10)] between the control groups and the test compound-administered groups.

The results are shown in Table 5.

Table 5

Test Compound	Dose (mg/kg,ip)	Amount of creatinine in blood serum (mg/dl)	Amount of urea nitrogen in blood serum (mg/dl)
Control group	-	4.55±0.24	137.2±5.0
1	0.03	2.51±0,41***	81.4±15.9*1)
2	0.03	2.51±0.24***	85.0±8.7***
4	0.03	2.32±0.48**	75.6±13.9**1)
5	0.1	2.34±0.24***	74.4±7.7***
Control group	-	3.90±0.24	124.9±7.5
6	0.01	2.23±0.15***	65.4±5.6***
7	0.01	2.28±0,22***	70.0±9.8***
Control group	-	4.35±0.23	139.7±10.2
3	0.01	2.00±0.21**2)	69.9±8.4**2)
3	0.1	2.32±0.16**2)	64.4±4.5**2)

**p<0.01;
***p<0,001(Student's t test);
1) **p<0.01(Aspin-Welch test);
2)**p<0.01(Dunnett's test)

Table 5 showed that test compounds administered intraperitoneally at a dose of 0.1 mg/kg or lower, significantly inhibited the increase in the amount of creatinine and that the amount of urea nitrogen in blood serum.

On the contrary, aminophylline (10 mg/kg, i.p.) showed a weak effect of suppressing the increase, and furosemide (10 mg/kg, i.p.) showed a tendency to increase the serum creatinine.

Test Example 5 Activity on (R)-PIA-Induced Amnesia

The anti-dementia effect of Compound (I) was determined using the (R)-PIA [(R)-N^6-(2-phenylisopropyl)adenosine]-induced dementia model [Jpn. J. Pharmacol. 52 (Suppl.II), 107P (1990)] As the experimental animal, groups of ddY-strain mice (weighing 20 - 25 g), each group consisting of fifteen mice, were used. The test was performed with a step-through type passive avoidance apparatus (the bright and dark box).

The bright and dark box was made up of a bright compartment (15 × 9 × 11 cm) lighted by 4W white fluorescent light and a dark compartment (15 × 14 × 18 cm). These two compartments were partitioned by a guillotine door (3 × 3 cm) and had a grid floor of stainless steel. In order to give a foot shock, an electric current (0.3 mA: 2 sec) may be passed through the grid floor of the dark compartment.

The compound to be tested was suspended in 0.3% aqueous solution of carboxymethyl cellulose (CMC) and the suspension was orally administered 60 minutes before the acquisition trial (to the normal control group and the amnesia control group which is subjected to the following amnesia treatment, only 0.3 % CMC was administered). 30 minutes after the administration of the test compound, 0.3 mg/kg of (R)-PIA was administered intraperitoneally as amnesia-inducing treatment [(R)-PIA was not administered to the normal control group].

The training for acquisition of learning (acquisition trial) was carried out. The rat was introduced into the bright compartment, and after 10 seconds, the guillotine door was opened. The rat in the bright compartment rapidly moved into the dark compartment. As soon as the whole body of the rat entered the dark compartment, the guillotine door was closed and an electric current of 0.3 mA was passed through the grid floor for 2 seconds (foot shock). Immediately

after the foot shock, the rat was taken out of the dark compartment.

The test trial for observing the retention and recall of the memory (recall trial) was carried out as follows. Twenty-four hours after the acquisition trial, the rat was placed in the bright compartment and the guillotine door was opened. The length of time before the rat entered the dark compartment (latency) was measured. The latency was measured up to 600 seconds and the latency longer than 600 seconds was recorded as 600 seconds.

The anti-dementia effect was judged from whether or not the reaction latency of the test compound-administered group was significantly increased from the reaction latency of the amnesia control group. The test of significance was carried out by the Steel-test. The results are shown in Table 6.

Table 6

Test Compound	Dose (mg/kg; oral)	Amnesia treatment	Number of used animals	Recall trial average reaction latency (sec)	Comparison with amnesia control
normal control	-	-	15	560.0±26.6	-
amnesia control	-	+	15	51.5±17.0	-
Compound 3	0.08	+	15	404.3±43.5	$p < 0.01$
	0.31	+	15	438.8±43.0	$p < 0.01$
	1.25	+	15	445.5±49.5	$p < 0.01$
	5.0	+	15	430.5±43.2	$p < 0.01$

As seen from Table 6, oral administration of Compound (I) at a dose of 5 mg/kg or lower resulted in an anti-dementia effect.

Compounds (I) or the pharmaceutically acceptable salts thereof can be administered as they are, or in the form of various pharmaceutical compositions. The pharmaceutical compositions in accordance with the present invention can be prepared by uniformly mixing an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient, with a pharmaceutically acceptable carrier. It is desired that such pharmaceutical compositions are prepared in a unit dose form suitable for oral administration or administration through injection.

For preparing a pharmaceutical composition for oral administration, any useful pharmaceutically acceptable carrier can be used. For example, liquid preparations for oral administration such as suspensions and syrups can be prepared using water, sugars such as sucrose, sorbitol, and fructose, glycols such as polyethylene glycol and propylene glycol, oils such as sesame oil, olive oil, and soybean oil, preservatives such as p-hydroxybenzoates, flavors such as strawberry flavor and peppermint, and the like. Powders, pills, capsules, and tablets can be prepared using excipients such as lactose, glucose, sucrose, and mannitol, disintegrators such as starch and sodium alginate, lubricants such as magnesium stearate and talc, binders such as polyvinyl alcohol, hydroxypropyl cellulose, and gelatin, surfactants such as fatty acid esters, plasticizers such as glycerin, and the like. Tablets and capsules are the most useful oral unit dose forms because of the readiness of administration. For preparing tablets and capsules, solid pharmaceutical carriers are used.

Injectable preparations can be prepared using a carrier such as distilled water, a salt solution, a glucose solution or a mixture of a salt solution and a glucose solution. The preparations can be prepared in the form of solution, suspension, or dispersion according to a conventional method by using a suitable solubilizing agent or suspending agent.

Compound (I) or the pharmaceutically acceptable salt thereof can be administered orally in the dosage forms or parenterally as injections. The effective dose and the administration schedule vary depending upon the mode of administration, the age, body weight, and conditions of a patient, etc. However, generally, Compound (I) or a pharmaceutically acceptable salt thereof is administered in a daily dose of 1 to 50 mg/kg in 3 to 4 portions.

Certain embodiments of the invention are illustrated in the following examples, preparation examples and reference examples.

Example 1

8-(9-Oxo-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1,3-dipropylxanthine (Compound 1)

A suspension of Compound E (250 mg, 0.644 mmol) obtained in Reference Example 1 and calcium hydroxide (334 mg, 4.51 mmol) in 4 ml of water was heated under reflux for 30 minutes. The mixture was cooled, adjusted to pH

2 with concentrated hydrochloric acid and extracted three times with chloroform. The extracts were washed with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was recrystallized from ethanol/water, to give 141 mg (yield 59 %) of Compound 1 as a white plate crystal.

Melting Point: 172.0-173.7 °C

Elemental Analysis: $C_{20}H_{26}N_4O_3$			
Calcd. (%)	C, 64.85;	H, 7.07;	N, 15.12
Found (%)	C, 64.43;	H, 7.33;	N, 15.21

IR(KBr) ν_{max} (cm^{-1}) : 1703, 1650, 1560, 1501.
NMR(270MHz; $CDCl_3$) δ(ppm) :
12.14(1H, brs), 4.12(2H, t, J=7.3Hz), 3.97(2H, t, J=7.6Hz), 3.16(1H, t, J=5.9Hz), 2.89(2H, brs), 2.60-2.53(2H, m), 2.34-2.23(4H, m), 1.98-1.93(2H, m), 1.90-1.60(4H, m), 0.98(3H, t, J=7.0Hz), 0.94(3H, t, J=7.3Hz).
MS(EI)m/e(relative intensity) :
370(100,M^+), 328(53), 300(46), 286(54), 258(35), 256(37), 217(41).

Example 2

8-(6-Oxo-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1,3-dipropylxanthine (Compound 2)

Substantially the same procedure as in Example 1 was repeated using Compound F (570 mg, 1.47 mmol) obtained in Reference Example 1 as a starting compound, instead of Compound E, to give 478 mg (yield 79 %) of Compound 2 as a white powder.
Melting Point: 162.8-164.1 °C

Elemental Analysis: $C_{20}H_{26}N_4O_3$			
Calcd. (%)	C, 64.85;	H, 7.07;	N, 15.12
Found (%)	C, 64.56;	H, 7.28;	N, 15.21

IR(KBr) ν_{max}(cm^{-1}) : 1751, 1703, 1648, 1556, 1508, 1502.
NMR(270MHz; $CDCl_3$) δ(ppm) :
12.18(1H, brs), 4.09(2H, t, J=7.2Hz), 4.02(2H, t, J=7.8Hz), 3.07(1H, dd, J=7.9, 1.7Hz), 2.68-2.60(1H, m), 2.60-1.85 (9H, m), 1.80-1.60(4H, m), 0.97(6H, t, J=7.3Hz).
MS(EI)m/e (relative intensity) :
370(100,M^+), 328(61), 300(51), 286(86), 258(39), 256(36), 217(13).

Example 3

8-(Trans-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1,3-dipropylxanthine (Compound 3) and 8-(cis-9-hydroxy-3-tricyclo [3.3.1.$0^{3,7}$]nonyl)-1,3-dipropylxanthine (Compound 4)

To a solution of 70.0 mg (0.189 mmol) of Compound 1 obtained in Example 1 in 3 ml of ethanol, 9.2 mg (0.378 mmol) of lithium borohydride was added under ice-cooling, and stirred at room temperature for 1.5 hours. The resulting mixture was acidified with 1N hydrochloric acid to pH 3, and extracted three times with chloroform. The combined extracts were washed with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by high performance liquid chromatography (HPLC) [column:YMC-Pack, SH-365-10, S-10 [YMC Co., Ltd.] 30mmi.d.x500 mm; eluent: 50 % acetonitrile/water; flow rate: 80 ml/min] to give 26.6 mg (yield 38 %) of Compound 3 and 11.5 mg (yield 16 %) of Compound 4, as a white powder.

Compound 3:

Melting Point: 224.9-225.3 °C

Elemental Analysis: $C_{20}H_{28}N_4O_3$			
Calcd. (%)	C, 64.49;	H, 7.58;	N, 15.04
Found (%)	C, 64.74;	H, 7.37;	N, 15.15

IR(KBr) ν_{max} (cm^{-1}) : 1696, 1653, 1555, 1508, 1495.
^{1}H-NMR(270MHz; CD_3OD) δ(ppm) :
4.07(2H, m), 3.95(2H, m , 3.89(1H, m), 2.62(1H, m), 2.34(2H, m), 2.17(2H, m), 2.10(2H, m), 1.98(2H, dd, J=10.9, 2.7Hz), ca. 1.81(2H, m), 1.77(2H, m), 1.66(2H, m), 0.95(3H, t, J=7.4Hz), 0.94(3H, t, J=7.4Hz).
^{13}C-NMR(270MHz; CD_3OD) δ(ppm) :
161.8, 156.1, 153.0, 149.8, 108.4, 73.2, 49.5, 46.6, 46.3, 46.1, 44.9, 43.9, 39.7, 22.41, 22.36, 11.5, 11.4.
MS(EI)m/e(relative intensity) :
372(100,M$^+$), 330(59), 302(27), 288(63), 258(17).

Compound 4:

Melting Point: 224.8-225.1 °C

Elemental Analysis: $C_{20}H_{28}N_4O_3$			
Calcd. (%)	C, 64.49;	H, 7.58;	N, 15.04
Found (%)	C, 64.58;	H, 8.01;	N, 14.94

IR(KBr) ν_{max} (cm^{-1}) :1694, 1650, 1499.
^{1}H-NMR(270MHz; CD_3OD) δ(ppm):
4.08(2H, m), 3.95(2H, m), 3.86(1H, m), 2.68(1H, bt, J=6.6Hz), 2.36(2H,m), ca. 2.35(2H, m), 2.01-1.90(4H, m), 1.78(2H, m), 1.66(2H, m), ca. 1.65(2H, m), 0.96(3H, t, J=7.4Hz), 0.94(3H, t, J=7.4Hz).
^{13}C-NMR(270MHz; CD_3OD) δ(ppm) :
161.9, 156.1, 153.0, 149.8, 108.4, 72.7, 49.8, 46.1, 45.2, 45.1, 44.8, 43.9, 41.3, 22.41, 22.35, 11.5, 11.3.
MS(EI)m/e(relative intensity) :
372 (100,M$^+$), 330(26), 302(10), 288(44), 258(18).

Example 4

8-(Trans-6-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-1,3-dipropylxanthine (Compound 5)

Substantially the same procedure as in Example 3 was repeated using 75.0 mg (0.203 mmol) of Compound 2 obtained in Example 2 as a starting compound. The obtained crude product was recrystallized from ethanol/water to give 56.8 mg (yield 75 %) of Compound 5 as a white powder.
Melting Point: 192.8-193.5 °C

Elemental Analysis: $C_{20}H_{28}N_4O_3$			
Calcd. (%)	C, 64.49;	H, 7.58;	N, 15.04
Found (%)	C, 64.78;	H, 7.81;	N, 15.20

IR(KBr) ν_{max} (cm^{-1}) : 1703, 1654, 1553, 1500.
^{1}H-NMR (270 MHz; CD_3OD) δ(ppm):
4.22(1H, dd, J=6.9, 3.3Hz), 4.07(2H, m), 3.95(2H, m), 2.59(1H, tt, J=6.9, 1.3Hz), 2.51(1H, dd, J=11.4, 2.1Hz), 2.30(1H,m), ca. 2.18(2H, m), 2.10(1H, m), ca. 2.02(1H, m), ca. 1.97(1H, m), 1.91(1H, d, J=11.5Hz), 1.78(2H, m), 1.66 (2H, m), ca. 1.55(1H, m), ca. 1.48(1H, m), 0.95(3H, t, J=7.4Hz), 0.94(3H, t, J=7.4Hz).
^{13}C-NMR (270 MHz; CD_3OD) δ(ppm) :
161.9, 156.1, 153.0, 149.8, 108.4, 76.5, 49.4, 49.3, 46.1, 43.9, 43.7, 41.9, 38.2, 34.1, 30.4, 22.4, 22.3, 11.5, 11.3.
MS(EI)m/e(relative intensity) :
372(100, m$^+$), 370(81), 354(44), 330(50), 328(54), 288(81), 286(64).

Example 5

8-(Trans-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1,3-dipropylxanthine (Compound 3)

1) Preparation of rat hepatocyte microsome

Phenobarbital Sodium (product of Wako Pure Chemical Industries, Ltd.) was intraperitoneally administered to male rats (SD strain, SLC, 200-220g) at a dose of 80 mg/kg, once a day for 3 days. The liver was taken out of the rat on the fourth day, and suspended in ice-cooled 1.15 % potassium chloride-0.01M phosphate buffer (pH 7.4), having the 3-fold volume of the weight of the liver, with a Teflon homogenizer. The suspension was centrifuged (10,000 x g, 10 minutes, 4 °C), and the supernatant was further centrifuged (105,000 x g, 60 minutes, 4 °C). The precipitate was suspended again in the same amount of 1.15 % potassium chloride-0.01 M phosphate buffer (pH 7.4), and centrifuged (40,000 x g, 30 minutes, 4 °C). The precipitate thus obtained was suspended in 20 % glycerol and 0.1 mM disodium ethylenediamine tetraacetate (EDTA)-0.01M phosphate buffer (pH 7.4) to a final concentration of 10 mg (wet weight)/ml to give rat hepatocyte microsomes.

2) Synthesis of Compound 3 by use of the rat hepatocyte microsome

3.6 mg (0.01 mmol) of 8-(3-noradamantyl)-1,3-dipropylxanthine[1,3-dipropy1-8-(3-tricyclo[3.3.1.$0^{3,7}$]nonyl) xanthine (as described in Japanese Published Unexamined Patent Application No. 173889/91) was dissolved in 1 ml of methanol, and 10 ml of the previously obtained rat hepatocyte microsome, 5 ml of 4 % bovine serum albumin (BSA)/0.2 M phosphate buffer (pH 7.4), 2 ml of NADPH-generating reaction mixture [8 mM sodium β-nicotinamide adenine dinucleotide phosphate (β-NADP), 80 mM sodium glucose-6-phosphate, 10 units of glucose 6-phosphate dehydrogenase (derived from yeast: Oriental Yeast Co., Ltd.) and 60 mM magnesium chloride] and 2 ml of 1 mM EDTA were added, and the mixture was incubated at 37 °C for 1 hour. The reaction mixture was centrifuged (40,000 x g, 30 minutes, 4 °C), and the supernatant was collected, and the precipitate was suspended once again in 0.2 M phosphate buffer. To the suspension, 5 ml of 4 % bovine serum albumin (BSA)/0.2 M phosphate buffer (pH 7.4), 2 ml of an NADPH-generating reaction mixture [8 mM β-NADP, 80 mM glucose-6-phosphate, 10 units of glucose 6-phosphate dehydrogenase (derived from yeast: Oriental Yeast Co., Ltd.) and 60 mM magnesium chloride] and 2 ml of 1 mM EDTA were added once again and centrifuged again (40,000 x g, 30 minutes, 4 °C) and the supernatant was obtained. The procedure was repeated further four times, and all the supernatants were combined, and 600 µl of an aqueous 2N sodium hydroxide and 20 ml of ethyl acetate were added, and the mixture was shaken and stirred. The organic layer was separated by centrifugation (2500 rpm x 5 minutes) and concentrated. The residue was purified by HPLC [column:YMC AM-312(ODS) 5 µm [YMC Co., Ltd.] 6 mmi.d. x 150 mm; eluent: 40 % acetonitrile/an aqueous 50 mM ammonium acetate; flow rate: 1 ml/min], to give ca. 400 µg (yield ca. 10 %) of Compound 3 as a white powder.

Example 6

3-(3-Hydroxypropyl)-8-(3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1-propylxanthine (Compound 6) and 3-(2-hydroxypropyl)-8-(3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1-propylxanthine (Compound 7)

100 mg (0.282 mmol) of Compound H obtained in Reference Example 2 was dissolved in 1 ml of tetrahydrofuran. To the solution diborane-dimethylsulfide complex (10 M tetrahydrofuran solution, 28µl,0.28 mmol) was added dropwise, and the resulting mixture was stirred at room temperature for 1 hour. After cooling to 0 °C, 1 ml of ethanol, 330 µl of aqueous 2N sodium hydroxide and 250 µl of aqueous 35 % hydroperoxide were added and the resulting mixture was again stirred at room temperature for 1 hour. The reaction mixture was neutralized and extracted three times with chloroform. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give 106 mg of a ca. 6:4 mixture (quantitatively) of Compound 6 and Compound 7 as a white powder.

The mixture was purified by HPLC [column:YMC Pack D-ODS-5[YMC Co., Ltd.] 250 mm x 20 mm; eluent : 50 % acetonitrile/water; flow rate:13 ml/min.] to give 31.9 mg of Compound 6 and 21.4 mg of Compound 7, as a white powder.

Compound 6:

Melting Point: 155.0-156.0 °C (recrystallized from ethanol/water)

Elemental Analysis: $C_{20}H_{28}N_4O_3$			
Calcd. (%)	C, 64.49;	H, 7.58;	N, 15.04

(continued)

Elemental Analysis: $C_{20}H_{28}N_4O_3$			
Found (%)	C, 64.56;	H, 7.76;	N, 14.73

IR(KBr) ν_{max} (cm^{-1}) :3400, 3180, 1700, 1653, 1506.
NMR(270MHz; $CDCl_3$) δ(ppm) :
11.79 (1H, brs), 4.31(2H, t, J=5.4Hz), 4.00(2H, t, J=7.4Hz), 3.49(2H, t, J=5.4Hz), 2.78(1H, t, J=6.4Hz), 2.50-2.40 (2H, m), 2.30-2.20(2H, m), 2.15-1.70(13H, m), 0.96(3H, t, J=7.4Hz).

Compound 7:

Melting Point: 220.0 - 222.0 °C (recrystallized from methanol)

Elemental Analysis: $C_{20}H_{28}N_4O_3$			
Calcd. (%)	C, 64.49;	H, 7.58;	N, 15.04
Found (%)	C, 63.97;	H, 7.81;	N, 14.75

IR(KBr) ν_{max} (cm^{-1}) :3470, 3180, 1701, 1632, 1500.
NMR(270MHz; $CDCl_3$) δ(ppm):
4.50-4.40(1H, m), 4.35-4.15(2H, m), 4.00(2H, t, J=7.4Hz), 2.78(1H, t, J=6.5Hz), 2.45-1.50(15H, m), 1.28(3H, d, J=6.0Hz), 0.96(3H, t, J=7.4Hz)

Example 7

8-(3-Hydroxy-1-tricyclo[3.3.1.$1^{3,7}$]decyl)-1-3-dipropylxanthine (Compound 8)

To a solution of 1.10 g (5.61 mmol) of 3-hydroxy-1-adamantane carboxylic acid (3-hydroxy-1-tricyclo [3.3.1.$1^{3,7}$] decane carboxylic acid)[Syn. Commun. 18, 1967 (1988)] in a mixture of 10 ml-methylene chloride and 25 ml-dimethyl formamide, 1.03 g(6.73 mmol) of 1-hydroxy benzotriazole and 1.61 g (8.42 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide were added and stirred at room temperature for 30 minutes. To the reaction mixture 15 ml of a solution of 5,6-diamino-1,3-dipropyluracil in methylene chloride was added dropwise under icecooling and with stirring, and the resulting mixture was stirred at room temperature for 1 hour. 50 ml of a saturated aqueous sodium bicarbonate solution was added to the resulting mixture and extracted three times with chloroform. The combined organic layer was washed twice with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. A suspension of the obtained residue and calcium hydroxide (2.77 g, 37 mmol) in 35 ml of water was heated under reflux for 3 hours. The mixture was then cooled, adjusted to pH 2 with concentrated hydrochloric acid, and extracted three times with chloroform. The extracts were washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 4 % methanol/chloroform), and recrystallized from hexane/toluene to give 680 mg (yield 33 %) of Compound 8 as a white plate crystal.
Melting Point: 213.1-214.3 °C

Elemental Analysis: $C_{21}H_{30}N_4O_3$			
Calcd. (%)	C, 65.26;	H, 7.82;	N, 14.50
Found (%)	C, 65.13;	H, 8.08;	N, 14.54

IR(KBr) ν_{max} (cm^{-1}) :
3510, 3148, 2906, 1703, 1637, 1544, 1494.
NMR(270MHz; DMSO-d_6) δ(ppm):
12.96(1H, brs), 4.56(1H, s), 3.94(2H, t, J=7.5Hz), 3.83(2H, t, J=7.3Hz), 2.19(2H, brs), 1.90-1.48(16H,m), 0.86 (3H, t, J=7.4Hz), 0.85(3H, t, J=7.4Hz).

Example 8

1-(2-Oxopropyl)-8-(3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthine (Compound 9)

Substantially the same procedure as in Example 1 was repeated using 1.70 g (4.38 mmol) of Compound I obtained in Reference Example 3 as a starting compound. The obtained crude product was recrystallized from acetone/water to give 874 mg (yield 54 %) of Compound 9 as a white plate crystal.
Melting Point: 210.8-212.5 °C

Elemental Analysis: $C_{20}H_{26}N_4O_3$			
Calcd. (%)	C, 64.85;	H, 7.07;	N, 15.12
Found (%)	C, 65.21;	H, 7.47;	N, 15.19

IR(KBr) ν_{max} (cm^{-1}) :1720(sh), 1700, 1655, 1553, 1499.
^{1}H-NMR(270MHz; $CDCl_3$) δ(ppm):
4.83(2H, s), 4.09(2H, t, J=7.5Hz), 2.74(1H, t, J=6.9Hz), 2.39(2H, brs), 2.25(3H, s), 2.27-2.20(2H, m), 1.95-1.60 (10H, m), 0.96(3H, t, J=7.4Hz).
MS(EI) m/e(rel.intensity):370(M^+, 100), 327(86).

Example 9

1-(2-Hydroxypropyl)-8-(3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthine (Compound 10)

Substantially the same procedure as in Example 3 was repeated using 780 mg (2.11 mmol) of Compound 9 obtained in Example 8. The obtained crude product was recrystallized from acetonitrile to give 440 mg (yield 56 %) of Compound 10 as a white prismatic crystal.
Melting Point: 194.7-196.9 °C

Elemental Analysis: $C_{20}H_{28}N_4O_3$			
Calcd. (%)	C, 64.49;	H, 7.58;	N, 15.04
Found (%)	C, 64.59;	H, 7.84;	N, 15.07

IR(KBr) ν_{max} (cm^{-1}) :1703, 1655, 1553, 1497.
^{1}H-NMR(270MHz; $CDCl_3$) δ(ppm):
10.84(1H, brs), 4.17-4.06(5H, m), 3.23(1H, d, J=4.9Hz), 2.76(1H, t, J=6.9Hz), 2.41(2H, brs), 2.22-2.18(2H, m), 2.05-1.68(10H, m), 1.26(3H, d, J=5.6Hz), 0.97(3H, t, J=7.4Hz).
^{13}C-NMR(270MHz; CD_3OD) δ(ppm) :
162.4, 156.2, 153.3, 149.8, 108.2, 66.6, 50.7, 49.8, 48.9, 46.9, 46.0, 44.7, 39.0, 35.7, 22.4, 21.1, 11.4.
MS(EI) m/e(rel. intensity):
372(M^+, 12), 354(21), 328(19), 315(100), 279(22).

Example 10

1-(3-Oxopropyl)-8-(3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthine (Compound 11)

A solution of 35.0 mg (0.10 mmol) of Compound J obtained in Reference Example 4 in 3 ml of N,N-dimethylformamide was added dropwise to a mixture of 0.5 ml-N,N-dimethylformamide and 0.5 ml-water containing 3.6 mg (0.02 mmol) of palladium chloride and 2.7 mg (0.02 mmol) of cupric chloride. The reaction mixture was stirred at 50 °C for 2 hours in an oxygen atmosphere, poured into 20 ml of ice water, extracted three times with chloroform. The extracts were washed with water, and with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to give 10.4 mg (yield 28 %) of 1-(2-oxopropyl)-8-(3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthine (Compound 9) and 9.9 mg (yield 27 %) of Compound 11, as a white powder.

Compound 11:

Melting Point: 180.9-183.8 °C
IR(KBr) ν_{max} (cm^{-1}) :1728(sh), 1699, 1657, 1554, 1495.
^{1}H-NMR(270MHz; $CDCl_3$) δ(ppm) :
11.40(1H, brs), 9.83(1H, s), 4.40(2H, t, J=7.0Hz), 4.09(2H, t, J=7.4Hz), 2.86-2.72(3H, m), 2.41(2H, brs), 2.22-2.18 (2H, m), 2.05-1.65(12H, m), 0.97(3H, t, J=7.4Hz). MS(EI) m/e: 370(M^+).

Example 11

8-(Trans-9-hydroxy-3-tricyclo[3.3,1.$0^{3,7}$]nonyl)-1-(2-oxopropyl)-3-propylxanthine (Compound 12), 8-(cis-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1-(2-oxopropyl)-3-propylxanthine (Compound 14) and 8-(trans-6-hydroxy-3-tricyclo [3.3.1.$0^{3,7}$]nonyl)-1-(2-oxopropyl)-3-propylxanthine (Compound 16)

Substantially the same procedure as in Example 1 was repeated using 208 mg (0.515 mmol) of a 1:1:8 mixture of Compound P, Compound Q and Compound R as obtained in Reference Example 5. The obtained crude product was purified by HPLC [Column: YMC-Pack, SH-365-10, S-10 [YMC Co., Ltd.] 30 mmi.d. × 500 mm; eluent: 25% acetonitrile/ water; flow rate: 40 ml/min] to give 12.9 mg (yield: 6.5%) of Compound 12, 9.3 mg (yield: 4.7%) of Compound 14 and 90.4 mg (yield: 46%) of Compound 16, as a white powder.

Compound 12:

Melting point: 254.8-256.8°C
IR(KBr) ν_{max} (cm^{-1}) :1720(sh), 1703, 1655, 1499.
^{1}H-NMR(270MHz; CD_3OD) δ(ppm) :
4.84(2H, s), 4.07(2H, t, J=7.4Hz), 3.89(1H, m), 2.63(1H, t, J=7.0Hz), 2.33(2H, m), 2.24(3H, s), 2.17(2H, m), 2.10 (2H, m), 1.99(2H, dd, J=10.9, 2.8Hz), 1.85-1.70(4H, m), 0.95(3H, t, J=7.4Hz).
MS(EI) m/e: 386 (M^+).

Compound 14:

Melting point: 238.1-241.8°C
IR(KBr) ν_{max} (cm^{-1}) :1718(sh), 1705, 1650, 1494.
^{1}H-NMR(270MHz; CD_3OD) δ(ppm) :
4.83(2H, s), 4.07(2H, t, J=7.4Hz), 3.86(1H, m), 2.68(1H, t, J=6.4Hz), 2.36(2H, m), 2.35(2H, m), 2.23(3H, s), 2.01-1.90(4H, m), 1.77(2H, m), 1.65(2H, dd, J=11.3, 2.9Hz), 0.95(3H, t, J=7.4Hz).
MS(EI) m/e: 386 (M^+).

Compound 16:

Melting point: 214.6-215.7°C
IR(KBr) ν_{max} (cm^{-1}) :1720(sh), 1703, 1650, 1498.
^{1}H-NMR(270MHz; CD_3OD) δ(ppm) :
4.84(2H, s), 4.22(1H, dd, J=6.9, 3.0Hz), 4.07(2H, t, J=7.4Hz), 2.60(1H, t, J=6.7Hz), 2.51(1H, dd, J=11.3, 2.0Hz), 2.29(1H, m), 2.23(3H, s), 2.20(2H, m), 2.10(1H, m), 2.05-1.95(2H, m), 1.90(1H, d, J=11.9Hz), 1.77(2H, m), 1.60-1.52 (1H, m), 1.48(1H, m), 0.95(3H, t, J=7.4Hz).
MS(EI) m/e: 386 (M^+).

Example 12

1-(2-Hydroxypropyl)-8-(trans-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthine (Compound 13)

Substantially the same procedure as in Example 3 was repeated using 8.4 mg (0.0218 mmol) of Compound 12 as obtained in Example 11 and 1.0 mg (0.0265 mmol) of sodium borohydride to give 7.4 mg (yield 88%) of Compound 13 as a white powder.
Melting point: 210.2-214.8°C
IR(KBr) ν_{max} (cm^{-1}) : 1701, 1642, 1495.
^{1}H-NMR(270MHz; CD_3OD) δ(ppm) :

4.15-4.05(2H, m), 4.07(2H, t, J=7.4Hz), 3.95-3.86(1H, m), 3.88(1H, m), 2.61(1H, t, J=6.5Hz), 2.33(2H, m), 2.17 (2H, m), 2.10(2H, m), 1.97(2H, dd, J=10.4, 2.6Hz), 1.85-1.70(4H, m), 1.18(3H, d, J=7.0Hz), 0.95 (3H, t, J=7.4Hz).
MS(EI) m/e: 388 (M^+).

Example 13

1-(2-Hydroxypropyl)-8-(cis-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthine (Compound 15)

Substantially the same procedure as in Example 3 was repeated using 6.4 mg (0.0167 mmol) of Compound 14 as obtained in Example 11 and 1.0 mg (0.0265 mmol) of sodium borohydride to give 5.2 mg (yield: 80%) of Compound 15 as a white powder.
Melting point: 221.8-222.6°C
IR(KBr) ν_{max} (cm^{-1}) : 1706, 1645, 1500.
^{1}H-NMR(270MHz; CD_3OD) δ(ppm) :
4.15-4.05(2H, m), 4.07(2H, t, J=7.4Hz), 3.94-3.85(1H, m), 3.86(1H, m), 2.67(1H, t, J=6.4Hz), 2.35(2H, m), 2.34 (2H, m), 2.01-1.90(4H, m), 1.77(2H, m), 1.65(2H, dd, J=11.4, 3.0Hz), 1.18(3H, d, J=6.9Hz), 0.96(3H, t, J=7.4Hz).
MS(EI) m/e: 388 (M^+).

Example 14

1-(2-Hydroxypropyl)-8-(trans-6-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthine (Compound 17)

Substantially the same procedure as in Example 3 was repeated using 57.4 mg (0.149 mmol) of Compound 16 as obtained in Example 11 and 6.1 mg (0.161 mmol) of sodium borohydride to give 48.6 mg (yield: 84%) of Compound 17 as a white powder.
Melting point: 200.1-201.0°C
IR(KBr) ν_{max} (cm^{-1}) : 1699, 1647, 1498.
^{1}H-NMR(270MHz; CD_3OD) δ(ppm) :
4.22(1H, dd, J=6.9, 3.3Hz), 4.15-4.05(2H, m), 4.07(2H, t, J=7.4Hz), 3.89(1H, m), 2.58(1H, t, J=6.9Hz), 2.51(1H, dd, J=11.3, 2.0Hz), 2.30(1H, m), 2.20(2H, m), 2.10(1H, m), 2.05-1.95(2H, m), 1.91(1H, d, J=11.4Hz), 1.77(2H, m), 1.60-1.52(1H, m), 1.48(1H, m), 1.18(3H, d, J=7.0Hz), 0.95(3H, t, J=7.4Hz).
MS(EI) m/e: 388 (M^+).

Preparation Example 1 Tablet

Tablets comprising the following composition were prepared by a conventional method.
40 g of Compound 1, 286.8 g of lactose, and 60 g of potato starch were mixed and 120 g of aqueous 10 % hydroxypropylcellulose was added thereto. The resulting mixture was mixed, granulated and dried. The particle size was controlled. 1.2 g of magnesium stearate was added and mixed with the resulting granules and tablets (each tablet contains 20 mg of an active ingredient) were produced by tablet making machine having a striker of 8 mm diameter (RT-15 type manufactured by Kikusuisha).

Formulation	Compound 1	20 mg
	Lactose	143.4 mg
	Potato starch	30 mg
	Hydroxypropylcellulose	6 mg
	Magnesium stearate	0.6 mg
		200 mg

Preparation Example 2 Granule

Granules comprising the following composition were prepared by a conventional method.
20 g of Compound 3, 655 g of lactose and 285 g of corn starch were mixed and 400 g of 10 % aqueous hydroxypropylcellulose solution was added. The resulting mixture was mixed, granulated and dried, to provide granules. 20 mg of active ingredient was contained per 1,000 mg of the granules.

Formulation	Compound 3	20 mg
	Lactose	655 mg
	Corn starch	285 mg
	Hydroxypropylcellulose	40 mg
		1,000 mg

Preparation Example 3 Capsule

Capsules comprising the following composition were prepared by a conventional method.

200 g of Compound 6, 995 g of AVICEL and 5 g of magnesium stearate were mixed by a conventional method. The resulting mixture was filled in a hard capsule No.4 (with a volume of 120 mg per 1 capsule) by a capsule charger (LZ64 type manufactured by Zanashi Co.) to provide the capsules. 50 mg of active ingredient was contained per 1 capsule.

Formulation	Compound 6	20 mg
	AVICEL	99.5 mg
	Magnesium stearate	0.5 mg
		120 mg

Preparation Example 4 Injection

An injection comprising the following composition was prepared by a conventional method.

1 g of Compound 7 was dissolved in 100 g of refined soybean oil, and 12 g of refined egg yolk lecithin and 25 g of glycerin for injection were added. Injectable distilled water was added to make the total volume 1000 ml and the resulting mixture was mixed and emulsified by a conventional method. The resulting dispersion was filtered (sterile filtration) through a 0.2 μm disposable membrane filter, then injected in a glass vial under sterilized condition at a volume of 2 ml. The injection contained 2 mg of an active ingredient per 1 vial.

Formulation	Compound 7	2 mg
	Refined soybean oil	200 mg
	Refined egg yolk lecithin	24 mg
	Glycerin for injection	50 mg
	Distilled water for injection	1.72 ml
		2.00 ml

Reference Example 1

6-Amino-5-(9-oxo-3-tricyclo[3.3,1.$0^{3,7}$]-nonylcarbonylamino)-1,3-dipropyluracil (Compound E) and 6-amino-5-(6-oxo-3-tricyclo[3.3.1.$0^{3,7}$]nonylcarbonylamino)-1,3-dipropyluracil (Compound F)

To a solution of 6.95 g(38.6mmol) of tricyclo[3.3.1.$0^{3,7}$]nonane-3-carboxylic acid methyl ester in 175 ml of anhydrous acetic acid and 70 ml of glacial acetic acid, 23.1 g (231 mmol) of chromic anhydride in 35 ml-water was added under ice-cooling over a one-hour period (the inside temperature: 10-15 °C) and stirred at room temperature for 3 days. The resulting mixture was poured into 3 ℓ of ice-water and extracted three times with 200 ml portions of ether. The combined organic layer was washed with water, with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give 1.64 g (yield 22 %) of a ca. 1:2 mixture of 9-oxotricyclo[3.3.1.$0^{3,7}$]nonane-3-carboxylic acid methyl ester (Compound A) and 6-oxotricyclo[3.3.1.$0^{3,7}$]nonane-3-carboxylic acid methyl ester (Compound B) as a pale yellow oily substance.

NMR(270MHz; $CDCl_3$) δ(ppm) :

3.76(3x1/3H, s, CO_2CH_3 of A), 3.72(3x2/3H, s, CO_2CH_3 of B), 2.98(1x1/3H, t, J=6.3Hz, C7-H of A), 2.81-2.79 (1x/3H, m, C7-H of B), 2.79-2.76 (2x1/3H, m, Cl-H and C5-H of A), 2.55-2.45(2x2/3H, m, C1-H and C5-H of B), 2.35-1.82 (8H, m).

^{13}C-NMR(270MHz; $CDCl_3$) δ(ppm):

215.2(C=O of B), 212.2(C=O of A), 175.9($C^*O_2CH_3$ of A), 175.3($C^*O_2CH_3$ of B), 52.7(C3 of A), 52.1(C1 and C5 of A), 52.1 ($CO_2C^*H_3$ of A), 52.0($CO_2C^*H_3$ of B), 51.9(C7 of B), 50.3(C3 of B), 48.0(C5 of B), 46.6(C2 and C4 of A), 46.0(C4 of B), 45.2(C2 of B), 43.5(C6 and C8 of A), 42.7(C7 of A), 39.4(C8 of B), 37.0(C9 of B), 36.3(C1 of B).

To a solution of 1.04 g (8.45 mmol) of a ca. 1:2 mixture of Compound A and Compound B as obtained above in 30 ml of methanol, 1.42 g(33.8 mmol) of lithium hydroxide in 15 ml of water was added. The mixture was stirred at room temperature for 2 hours. The resulting mixture was adjusted to pH 3 with concentrated hydrochloric acid, and extracted 4 times with 20 ml portions of ether. The combined extracts were washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 1.38 g (yield 90 %) of a ca. 1:2 mixture of 9-oxotricyclo[3.3.1.$0^{3,7}$]nonane-3-carboxylic acid (Compound C) and 6-oxotricyclo[3.3.1.$0^{3,7}$]nonane-3-carboxylic acid (Compound D) as a colorless crystalline powder.

NMR(270MHz; $CDCl_3$) δ(ppm):

3.04(1x1/3H, t, J=6.0Hz), 2.84-2.81(1x2/3H, m), 2.80-2.76(2x1/3H, m), 2.60-2.45(2x2/3H, m), 2.35-1.75(8H, m).

To a solution of 1.00 g (5.56 mmol) of a ca. 1:2 mixture of Compound C and Compound D as obtained above in a mixture of 10 ml of methylene chloride and 25 ml of dimethyl formamide, 1.07 g (7.00 mmol) of 1-hydroxybenzotriazole and 1.10 g(8.34 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide were added and the mixture was stirred at room temperature for 30 minutes. 1.20 g (5.29 mmol) of 5,6-diamino-1,3-dipropyluracil in 15 ml of methylene chloride was added dropwise to the reaction mixture with stirring under ice-cooling, and the resulting mixture was stirred at room temperature for one hour. 50 ml of a saturated aqueous sodium bicarbonate solution was added to the resulting mixture, and extracted three times with chloroform. The combined organic layer was washed twice with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by HPLC (column:YMC-Pack, SH-365-10, S-10 [YMC Co., Ltd.] 30mmi. d. x 500 mm; eluent: 27.5 % acetonitrile/10mM ammonium acetate aqueous solution; flow rate : 80 ml/min] to give 298 mg (yield 15 %) of Compound E and 655 mg (yield 32 %) of Compound F, as a white powder.

Compound E:

Melting Point: 125.6-127.1 °C

IR(KBr) ν_{max} (cm^{-1}) : 3350(br), 1700, 1656, 1593, 1494.

NMR(270MHz; $CDCl_3$) δ(ppm) :

7.51(1H, brs), 5.54(2H, brs), 3.93-3.86(4H, m), 3.10(1H, t, J=6.2Hz), 2.84(2H, brs), 2.39-2.32(2H, m), 2.21-2.13 (4H, m), 1.93-1.88(2H, m), 1.85-1.60(4H, m), 1.02(3H, t, J=7.3Hz), 0.94 (3H, t, J=7.2Hz).

MS(EI)m/e(relative intensity) :

388(63, M^+), 225(100), 163(17).

MS(HR)m/e:

Calcd.($C_{20}H_{28}N_4O_4$) 388.2111; Found 388.2126

Compound F:

Melting Point: 179.7-181.2 °C

IR(KBr) ν_{max} (cm^{-1}) :3320(br), 1741, 1699, 1619, 1509.

NMR(270MHz; $CDCl_3$) δ(ppm) :

7.41(1H, brs), 5.50(2H, brs), 3.92-3.85(4H, m), 2.92(1H, dd, J=8.0, 1.8Hz), 2.61(1H, brs), 2.54(1H, brs), 2.44-1.55 (12H, m), 1.01(3H, t, J=7.4Hz), 0.93(3H, t, J=7.4Hz).

MS(EI)m/e(relative intensity) :

388(43, M^+), 370(16), 225(100), 183(18).

MS(HR)m/e:

Calcd. ($C_{20}H_{28}N_4O_4$) 388.2111; Found 388.2119

Reference Example 2

3-Allyl-1-propyl-8-(3-tricyclo[3.3.1.$0^{3,7}$]nonyl)xanthine (Compound H)

To a solution of 3.22 g (19.4 mmol) of tricyclo[3.3.1.$0^{3,7}$]nonane-3-carboxylic acid in 80 ml of pyridine, 1.54 ml(21.1 mmol) of thionyl chloride was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 50 minutes. 3.21 g (17.6 mmol) of 1-allyl-5,6-diaminouracil(USP No.2673848) was added slowly under ice-cooing and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and extracted 5 times with chloroform/methanol (5:1). The combined organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. 30 ml of dioxane and 60 ml of 1N sodium

hydroxide aqueous solution were added to the residue, and the mixture was heated under reflux for 30 minutes. The reaction mixture was cooled, neutralized and extracted three times with chloroform. The combined organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to give 4.92 g(yield 90 %) of 3-allyl-8-(3-tricyclo[3.3.1.$0^{3,7}$]nonyl)xanthine (Compound G) as a pale yellow plate crystal.
Melting Point: >270 °C (recrystallized from ethanol/water)

Elemental Analysis: $C_{17}N_{20}N_4O_2$			
Calcd. (%)	C, 65.36;	H, 6.45;	N, 17.93
Found (%)	C, 64.98;	H, 6.72;	N, 17.86

IR(KBr) ν_{max} (cm^{-1}) : 1685, 1648, 1643, 1498, 1425.
NMR(90MHz; $CDCl_3$) δ(ppm) :
12.10(1H, brs), 7.20(1H, s), 6.20-5.65(1H, m), 5.45-5.05(2H, m), 4.80-4.45(2H, m), 2.71(1H, t), 2.55-1.50(12H, m).

1.00g (3.21mmol) of Compound G was dissolved in 30 ml of dimethylformamide, and 256 mg of sodium hydride (60 %, 6.41 mmol) was added slowly to the solution at 0 °C. After 30 minutes, 0.33 ml(3.4 mmol) of 1-iodopropane was added dropwise slowly at the same temperature and stirred at room temperature overnight. The resulting reaction mixture was poured into 300 ml of water, neutralized and extracted three times with 100 ml of chloroform. The organic layer was washed with a saturated solution of aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluate: 30 % ethyl acetate/hexane) to give 225 mg (yield 20 %) of Compound H as a colorless needle crystal.
Melting Point: 196.2-197.1 °C (recrystallized from ethanol/water)

Elemental Analysis: $C_{20}H_{26}N_4O_2$			
Calcd. (%)	C, 67.77;	H, 7.39;	N, 15.80
Found (%)	C, 67.92;	H, 7.66;	N, 15.45

IR(KBr) ν_{max} (cm^{-1}) : 1704, 1646, 1499.
NMR(270MHz; $CDCl_3$) δ(ppm) :
6.15-5.90(1H, m), 5.40-5.20(2H, m), 4.75(2H, d, J=6.0Hz), 4.00(2H, t, J=7.4Hz), 2.80(1H, t, J=6.5Hz), 2.45-2.35 (2H, m), 2.30-2.20(2H, m), 2.10-1.85(4H, m), 1.75-1.55(6H, m), 0.95(3H, t, J=7.4Hz).

Reference Example 3

6-Amino-3-(2-oxopropyl)-5-(3-tricyclo[3.3.1.$0^{3,7}$]-nonylcarbonylamino)-1-propyluracil (Compound I)

To a solution of 2.20 g (6.63 mmol) of 6-amino-5-(3-tricyclo[3.3.1.$0^{3,7}$]nonylcarbonylamino)-1-propyluracil (Japanese Published Unexamined Patent Application No. 173889/91) in 35 ml of dimethylformamide, 3.24 g (9.95 mmol) of cesium carbonate, and 1.23 ml (13.3 mmol) of bromoacetone were added with stirring. The reaction mixture was stirred at 60 °C for 3.5 hours. The mixture was cooled, poured into 100 ml of water and extracted three times with 30 ml of chloroform. The organic layer was washed with 0.2M sodium thiosulfate aqueous solution, with water, with a saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluate: 2 % methanol/chloroform) to give 1.70 g (yield 66 %) of Compound I as a pale yellow powder.
IR(KBr) ν_{max} (cm^{-1}) : 1725(sh), 1701, 1637, 1491.
^{1}H-NMR(270MHz; $CDCl_3$) δ(ppm) :
7.28(1H, brs), 5.68(2H, brs), 4.74(2H, s), 3.88(2H, t, J=7.4Hz), 2.74(1H, t, J=7.0Hz), 2.37(2H, brs), 2.23 (3H, s), 2.12-2.08(2H, m), 1.92-1.55(10H, m), 1.00(3H, t, J=7.4Hz).
MS(EI) m/e(rel. intensity):388(M^+, 70), 149(100), 121(90).

Reference Example 4

1-Allyl-8-(3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthine (Compound J)

Substantially the same procedure as in Reference Example 3 was repeated using 300 mg (0.90 mmol) of 6-amino-5-(3-tricyclo[3.3.1.$0^{3,7}$]nonylcarbonylamino)-1-propyluracil (Japanese Published Unexamined Patent Application No.

173889/91) and 0.16 ml (1.81 mmol) of allyl bromide. The obtained crude product was subjected to the same cyclization reaction that was used in Example 1, without purification, to give 110 mg (yield 35 %) of Compound J as a white powder.
Melting Point: 190.8-191.5 °C
IR(KBr) ν_{max} (cm^{-1}) : 1703, 1651, 1553, 1550.
^{1}H-NMR (270MHz; $CDCl_3$) δ(ppm) :
11.5(1H, brs), 5.98-5.84(1H, m), 5.22-5.13(2H, m), 4.67-4.65(2H, m), 4.12(2H, t,J=7.4Hz), 2.78(1H, t, J=6.9Hz), 2.40(2H, brs), 2.27-2.23(2H, m), 2.06-1.64(10H, m), 0.97(3H, t, J=7.4Hz).
MS(EI) m/e: 354(M^+).

Reference Example 5

6-Amino-5-(trans-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]-nonylcarbonylamino)-3-(2-oxopropyl)-1-propyluracil (Compound P)

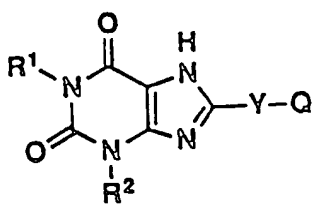
6-Amino-5-(cis-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]-nonylcarbonylamino)-3-(2-oxopropyl)-1-propyluracil (Compound Q)

6-Amino-5-(trans-6-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]-nonylcarbonylamino)-3-(2-oxopropyl)-1-propyluracil (Compound R)

Substantially the same procedure as in Reference Example 1 was repeated using a 613 mg (3.40 mmol) of a ca. 1:4 mixture of Compound C and Compound D obtained in Reference Example 1, and 597 mg (3.24 mmol) of 5,6-diamino-1-propyluracil (Japanese Published Unexamined Patent Application No. 173889/91). The obtained crude product was purified by silica gel column chromatography (eluent: 10% methanol/chloroform) to give 923 mg (yield: 82%) of a ca. 1:4 mixture of 6-amino-5-(9-oxo-3-tricyclo[3.3.1.$0^{3,7}$]nonylcarbonylamino)-1-propyluracil (Compound K) and 6-amino-5-(6-oxo-3-tricyclo[3.3.1.$0^{3,7}$]nonylcarbonylamino)-1-propyluracil (Compound L) as a white powder.
Melting Point: 269.6-272.2°C
IR(KBr) ν_{max} (cm^{-1}) : 1738, 1698, 1640, 1582, 1493.
MS(EI) m/e: 346(M^+).
Substantially the same procedure as in Example 3 was repeated using 920 mg (2.66 mmol) of a ca. 1:4 mixture of Compound K and Compound L, and 101 mg (2.66 mmol) of sodium borohydride. The obtained crude product was purified by silica gel column chromatography (eluent: 20% methanol/chloroform) to give 698 mg (yield: 75%) of a ca. 1:1:8 mixture of 6-amino-5-(trans-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonylcarbonylamino)-1-propyluracil (Compound M), 6-amino-5-(cis-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonylcarbonylamino)-1-propyluracil (Compound N) and 6-amino-5-(trans-6-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonylcarbonylamino)-1-propyluracil (Compound O) as a white powder.
Melting Point: 278.8-290.2°C
IR(KBr) ν_{max} (cm^{-1}) : 1695, 1612, 1486.
MS(EI) m/e: 348(M^+).
Substantially the same procedure as in Reference Example 3 was repeated using 696 mg (1.98 mmol) of a ca. 1:1:8 mixture of Compound M, Compound N and Compound O. The obtained crude product was purified by silica gel column chromatography (eluent: 10% methanol/chloroform) to give 208 mg (yield: 26%) of a ca. 1:1:8 mixture of Compound P, Compound Q and Compound R as a white powder.
Melting Point: 120.7-123.2°C
IR(KBr) ν_{max} (cm^{-1}) : 1730(sh), 1699, 1638, 1484.
MS(EI) m/e: 404(M^+).

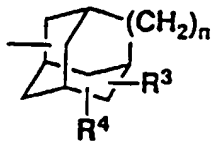
Claims

1. A xanthine compound represented by the formula (I)

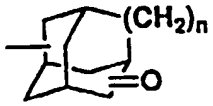


(I)

wherein R^1 and R^2 are the same or different and each represent hydroxy-substituted, oxo-substituted or unsubstituted straight or branched C_{1-6} alkyl, Y is a single bond or alkylene, and Q is



(wherein R^3 and R^4 are the same or different and each represent hydrogen or hydroxy, n is 0 or 1, and when both R^3 and R^4 are hydrogen, at least one of R^1 and R^2 is hydroxysubstituted or oxo-substituted straight or branched C_{1-6} alkyl), or



(wherein n has the same meaning as defined above); or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R^1 is hydroxy-substituted, oxo-substituted or unsubstituted propyl; R^2 is hydroxy-substituted or unsubstituted propyl; and Y is a single bond.

3. The compound according to claim 2, wherein R^1 is propyl, 2-hydroxypropyl, 2-oxopropyl or 3-oxopropyl; R^2 is propyl, 2-hydroxypropyl or 3-hydroxypropyl.

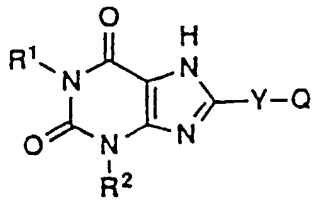
4. The compound according to any one of claims 1 to 3, wherein Q is 9-hydroxy, 9-oxo or 6-hydroxy substituted 3-tricyclo[3.3.1.$0^{3,7}$]nonyl, or 3-hydroxy-1-tricyclo[3.3.1.$1^{3,7}$]decyl.

5. The compound according to claim 1, which is selected from the group consisting of 8-(trans-9-hydroxy-3-tricyclo [3.3.1.$0^{3,7}$]nonyl)-1,3-dipropylxanthine, 8-(cis-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1,3-dipropylxanthine, 8-(trans-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1-(2-oxopropyl)-3-propylxanthine and 1-(2-hydroxypropyl)-8-(trans-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthine.

6. A pharmaceutical composition comprising the compound defined by any one of claims 1 to 5 as an active ingredient, and a pharmaceutically acceptable carrier.

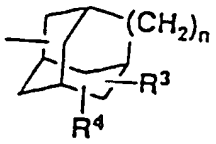
Patentansprüche

1. Xanthinverbindung der Formel (I)

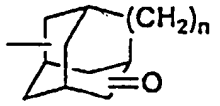


(I)

in der R^1 und R^2 gleich oder verschieden sind und jeweils einen hydroxysubstituierten, oxosubstituierten oder unsubstituierten linearen oder verzweigten C_{1-6}-Alkylrest darstellen, Y eine Einfachbindung oder ein Alkylenrest ist und Q



(wobei R^3 und R^4 gleich oder verschieden sind und jeweils ein Wasserstoffatom oder eine Hydroxylgruppe darstellen, n 0 oder 1 ist und wenn beide Reste R^3 und R^4 Wasserstoffatome sind, mindestens einer der Reste R^1 und R^2 ein hydroxysubstituierter oder oxosubstituierter linearer oder verzweigter C_{1-6}-Alkylrest ist), oder



ist (wobei n die vorstehend angegebene Bedeutung hat) oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, in der R^1 eine hydroxysubstituierte, oxosubstituierte oder unsubstituierte Propylgruppe ist; R^2 eine hydroxysubstituierte oder unsubstituierte Propylgruppe ist und Y eine Einfachbindung ist.

3. Verbindung nach Anspruch 2, in der R^1 eine Propyl-, 2-Hydroxypropyl-, 2-Oxopropyl- oder 3-Oxopropylgruppe ist; R^2 eine Propyl-, 2-Hydroxypropyl- oder 3-Hydroxypropylgruppe ist.

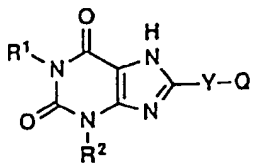
4. Verbindung nach einem der Ansprüche 1 bis 3, in der Q eine 9-hydroxy-, 9-oxo- oder 6-hydroxysubstituierte 3-Tricyclo[3.3,1.$0^{3,7}$]nonyl- oder 3-Hydroxy-1-tricyclo[3,3.1.$1^{3,7}$]decylgruppe ist.

5. Verbindung nach Anspruch 1, ausgewählt aus 8-(trans-9-Hydroxy-3-tricyclo-[3.3.1.$0^{3,7}$]nonyl)-1,3-dipropylxanthin, 8-(cis-9-Hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]-nonyl)-1,3-dipropylxanthin, 8-(trans-9-Hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1-(2-oxopropyl)-3-propylxanthin und 1-(2-Hydroxypropyl)-8-(trans-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthin.

6. Arzneimittel, umfassend die Verbindung nach einem der Ansprüche 1 bis 5 als Wirkstoff und einen pharmazeutisch verträglichen Träger.

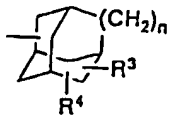
Revendications

1. Composé dérivé de la xanthine, représenté par la formule (I):

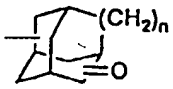


(I)

dans laquelle R^1 et R^2 sont identiques ou différents et représentent chacun un groupe alkyle en C_{1-6} linéaire ou ramifié, à substituant hydroxy ou oxo ou sans substituant, Y représente une simple liaison ou un groupe alkylène, et Q représente



(où R^3 et R^4 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe hydroxy et n vaut 0 ou 1, sous réserve que, si R^3 et R^4 représentent tous deux un atome d'hydrogène, au moins l'un des symboles R^1 et R^2 représente un groupe alkyle en C_{1-6} linéaire ou ramifié, à substituant hydroxy ou oxo,)
ou bien



(où n à la même signification que ci-dessus,)
ou sel d'un tel dérivé, admissible en pharmacie.

2. Composé conforme à la revendication 1, dans lequel R^1 représente un groupe propyle à substituant hydroxy ou oxo ou sans substituant, R^2 représente un groupe propyle à substituant hydroxy ou sans substituant, et Y représente une simple liaison.

3. Composé conforme à la revendication 2, dans lequel R^1 représente un groupe propyle, 2-hydroxypropyle, 2-oxopropyle ou 3-oxopropyle, et R^2 représente un groupe propyle, 2-hydroxypropyle ou 3-hydroxypropyle.

4. Composé conforme à l'une des revendications 1 à 3, dans lequel Q représente un groupe 3-tricyclo[3.3.1.$0^{3,7}$]nonyle portant un substituant 9-hydroxy, 9-oxo ou 6-hydroxy, ou un groupe 3-hydroxy-1-tricyclo[3,3.1,$1^{3,7}$]décyle.

5. Composé conforme à la revendication 1, qui est choisi dans l'ensemble que constituent la 8-(trans-9-hydroxy-3-tricyclo-[3.3.1.$0^{3,7}$]nonyl)-1,3-dipropylxanthine, la 8-(cis-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1,3-dipropylxanthine, la 8-(trans-9-hydroxy-3-tricyclo[3.3.1.$0^{3,7}$]nonyl)-1-(2-oxopropyl)-3-propylxanthine et la 1-(2-hydroxypropyl)-8-(trans-9-hydroxy-3-tricyclo-[3.3.1.$0^{3,7}$]nonyl)-3-propylxanthine.

6. Composition pharmaceutique comprenant, en qualité d'ingrédient actif, un composé conforme à l'une des revendications 1 à 5, ainsi qu'un véhicule admissible en pharmacie.